CHAPTER 7

STATISTICAL METHODS

This chapter summarizes the statistical approach used in the data analysis of the 1987 followup of the Air Force Health Study (AFHS). The statistical analysis emphasizes the evaluation of possible differences in health status between the Ranch Hand and Comparison group members. After preliminary analysis to check for data anomalies and to obtain a general overview of the data, the analysis comprised both simple contrasts between the two groups and more complex methods employing adjustment for important covariates. To augment these analyses, the possibility of a greater frequency of medical problems with increasing herbicide dose was assessed in the Ranch Hand group. The exposure index was used to approximate the potential herbicide exposure of each individual. The exposure index analyses paralleled the analyses of group contrasts and used the same candidate covariates. Further, longitudinal analyses were conducted for selected variables to examine group differences in the changes in these variables over time. A summary of the statistical techniques used is provided in Table 7-1. This basic approach was employed in the analyses for each clinical category.

The computer software used throughout for the more complex adjusted analyses included BMDP[1]®-LR and BMDP®-4F for discrete dependent variables, and SAS[2]® GLM for continuous dependent variables. During the analyses, assumptions underlying the statistical methods were checked and, if necessary, appropriate corrective steps were taken. For example, asymmetrically distributed data were transformed to enhance normality in continuous analyses and sparse cells were occasionally collapsed in discrete analyses.

PRELIMINARY ANALYSIS

The preliminary analysis included the calculation of basic descriptive measures for the dependent and independent variables (covariates) for each group (Ranch Hand and Comparison). The descriptive measures included frequency distributions, histograms, mean, median, standard deviation, and range. These analyses provided an overview of each variable and the relationship of the Ranch Hand group to the Comparison group. In addition, the preliminary analysis provided insight regarding the specification of normal/abnormal limits and cutpoints, and the choice of possible transformations of asymmetrically distributed data for continuous dependent variables.

Another purpose of the preliminary analysis was to examine the relationship between the covariates and the dependent variables and the relationships among the covariates. To accomplish this, cross tabulations of discrete variables were constructed and analyzed by the chi-square test or Fisher's exact test. For continuous variables, simple t-tests and analyses of variance were performed, and product-moment correlation coefficients were computed as appropriate. The preliminary analyses were accomplished with the use of SAS®. Covariate tables are presented for the dependent variable and relevant covariates and contain both descriptive statistics and corresponding p-values showing the strength and statistical significance of the associations. Associations with a p-value less than or equal to 0.05 are described as significant, and associations with a p-value greater than 0.05 but less than or equal to 0.10 are termed marginally significant or borderline significant.

TABLE 7-1.

Summary of Statistical Procedures

Chi-square Contingency Table Test

The chi-square test of independence[3] is calculated for a contingency table by the following formula:

$$\chi^2 = \Sigma(f_o - f_e)^2 / f_e$$

where the sum is taken over all cells of the contingency table and

f_o = observed frequency in a cell

f_e = expected frequency under the hypothesis of independence.

Large values indicate deviations from the null hypothesis and are tested for significance by comparing the calculated χ^2 to the tables of the chi-square distribution.

Correlation Coefficient (Pearson's Product-Moment)

The population correlation coefficient,[4] ρ, measures the strength of the linear relationship between two random variables X and Y. A commonly used sample-based estimate of this correlation coefficient is

$$r = \frac{\Sigma(x_i - \bar{x})(y_i - \bar{y})}{[\Sigma(x_i - \bar{x})^2 \Sigma(y_i - \bar{y})^2]^{1/2}}$$

where the sum is taken over all (x,y) pairs in the sample. A Student's t-test based on this estimator is used to test for a significant correlation between the two random variables of interest. For the sample size of 2,294 in this study, a sample correlation coefficient of ±0.041 is sufficient to attain a statistically significant correlation at a 5-percent level for a two-sided hypothesis test, assuming normality of X and Y.

Fisher's Exact Test

Fisher's exact test[3] is a randomization test of the hypothesis of independence for a 2x2 contingency table. This technique is particularly useful for small samples and sparse cells. This is a permutation test based on the exact probability of observing the particular set of frequencies, or of sets more extreme, under the null hypothesis. The p-value presented for this hypothesis test is twice the one-tail p-value[5] with an upper bound of 1. In most cases, this p-value is quite close to the p-value associated with the continuity-corrected chi-square test statistic.[5]

TABLE 7-1. (continued)

Summary of Statistical Procedures

General Linear Models Analysis

The form of the general linear model[6] for two independent variables is:

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

where

Y = dependent variable (continuous)

α = level of Y at $X_1 = 0$ and $X_2 = 0$, i.e., the intercept

X_1, X_2 = measured value of the first and second independent variables, respectively, which may be continuous or discrete

β_1, β_2 = coefficient indicating linear association between Y and X_1, Y and X_2, respectively; each coefficient reflects the effect on the model of the corresponding independent variable adjusted for the effect of the other independent variable

β_{12} = coefficient reflecting the linear interaction of X_1 and X_2, adjusted for linear main effects

ε = error term.

This model assumes that the error terms are independent and normally distributed with a mean of 0 and a constant variance. Extension to more than two independent variables and interaction terms is immediate.

Linear regression, multiple regression, analysis of variance, analysis of covariance, and repeated measures analysis of variance[7] are all examples of general linear models analyses.

Logistic Regression Analysis

The logistic regression model[3,8] enables a dichotomous dependent variable to be modeled in a regression framework with continuous and/or discrete independent variables. For two risk factors, such as group and age, the logistic regression model would be:

$$\text{logit } P = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \varepsilon$$

where

P = probability of disease for an individual with risk factors X_1 and X_2

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logit P = ln (P/1-P), i.e., the log odds for disease

X_1 = first risk factor, e.g., group

X_2 = second risk factor, e.g., age.

The parameters are interpreted as follows:

α = log odds for the disease when $X_1 = 0$ and $X_2 = 0$

β_1 = coefficient indicating the group effect adjusted for age

β_2 = coefficient indicating the age effect adjusted for group

β_{12} = coefficient indicating the interaction between group and age, adjusted for linear main effects

ϵ = error term.

In the absence of an interaction ($\beta_{12} = 0$), $\exp(\beta_1)$ reflects the adjusted odds ratio for individuals in Group 1 ($X_1 = 1$) relative to Group 0 ($X_1 = 0$). If the probability of disease is small, the odds ratio will be approximately equal to the relative risk.

Throughout this report, the adjusted odds ratios will be referred to as adjusted relative risks. Correspondingly, in the absence of covariates (i.e., unadjusted analysis), the odds ratios will be referred to as estimated relative risks.

Log-linear Analysis

Log-linear analysis[3] is a statistical technique for analyzing cross-classified data or contingency tables. A saturated log-linear model for a three-way table is:

$$\ln (Z_{ijk}) = U_o + U_{1(i)} + U_{2(j)} + U_{3(k)} + U_{12(ij)} + U_{23(jk)} + U_{13(ik)} + U_{123(ijk)}$$

where

Z_{ijk} = expected cell count

$U_{1(i)}$ = specific one-factor effect

$U_{12(ij)}$ = specific two-factor effect or interaction

$U_{123(ijk)}$ = three-factor effect or interaction.

TABLE 7-1. (continued)

Summary of Statistical Procedures

The simplest models are obtained by including only the significant U-terms. Adjusted relative risks are derived from the estimated U-terms from an adequately fitting model.

Proportional Odds Model Analysis

The proportional odds model[9] allows for the analysis of an ordered categorized dependent variable. The model assumes that the odds of falling below a certain level rather than above it for individuals at different levels of an independent variable $\underline{X}$ are in constant ratio. For example, if the response takes one of the four values "excellent," "good," "fair," or "poor," and $\underline{X}$ is a simple indicator variable designating group (Ranch Hand versus Comparison), then the proportional odds model states that the odds for responding "poor" versus "fair," "good," or "excellent" in the Ranch Hand group are a multiple, $\exp(\beta)$, of the corresponding odds in the Comparison group. Likewise, the odds for responding "poor" or "fair" versus "good" or "excellent" in the Ranch Hand group are the same multiple, $\exp(\beta)$, of the corresponding odds in the Comparison group, as are the odds for responding "poor," "fair," or "good" versus "excellent" in the two groups. Thus, the model is appropriate whenever one frequency distribution is "shifted left" relative to another distribution. Incorporation of other variables into $\underline{X}$ allows the estimation of proportional odds ratios adjusted for covariates.

Let the ordered response Y take values in the range 1 to K, and let $\pi_i(\underline{X})$, $i=1,\ldots,K$, denote the probability of responding at level i for an individual with covariate vector $\underline{X}$. Let $\kappa_j(\underline{X})$ be the odds that $Y \leq j$ given $\underline{X}$, i.e.,

$$\kappa_j(\underline{X}) = \frac{\pi_1(\underline{X}) + \pi_2(\underline{X}) + \ldots + \pi_j(\underline{X})}{\pi_{j+1}(\underline{X}) + \pi_{j+2}(\underline{X}) + \ldots + \pi_k(\underline{X})},\ j=1,\ldots,K-1$$

The proportional odds model specifies that

$$\kappa_j(\underline{X}) = \kappa_j \exp(\beta'\underline{X}),\ \text{for constant } \kappa_j.$$

Thus, the ratio of odds for individuals at covariate levels $\underline{X}_1$ and $\underline{X}_2$ is

$$\frac{\kappa_j(\underline{X}_1)}{\kappa_j(\underline{X}_2)} = \exp\{\beta'(\underline{X}_1 - \underline{X}_2)\}$$

and depends only on $\underline{X}_1 - \underline{X}_2$ and not on j.

TABLE 7-1. (continued)

Summary of Statistical Procedures

Two Sample t-Test

A statistical test for determining whether or not it is reasonable to conclude that two population means are unequal utilizes the t-distribution.[10] Tests can be performed when population variances are equal or unequal; different t-distributions are used, however. This test can be used when the two populations are independent (e.g., Ranch Hand and Comparison) or dependent (e.g., 1982 and 1987 measurements on the same participant for a longitudinal analysis).

GROUP CONTRASTS

Contrasts of the Ranch Hand and Comparison groups, termed core analyses, consisted of a series of steps taken to ascertain whether or not a statistically significant difference existed between these groups for every dependent variable examined.

Both unadjusted and adjusted analyses were performed and are presented for each clinical chapter. Unadjusted analyses consisted of contrasts between the Ranch Hand and Comparison groups of the mean values, or proportion with abnormal values, of each dependent variable by t-tests, Fisher's exact test, or chi-square tests, as appropriate. Adjusted analyses have taken into account significant covariates in the assessment of possible group differences using general linear, logistic regression, proportional odds, or log-linear models. Covariates measured in 1985 but not in 1987 were used where necessary. The terms significant, marginally significant, and borderline significant, as defined previously, are also used for the descriptions of the group contrast results and the adjusting models.

Continuous Dependent Variables

When the dependent variable was continuous, the general linear models procedure of SAS® was used to fit a model of the dependent variable in terms of group (Ranch Hand or Comparison), appropriate covariates, group-by-covariate interactions, and interactions between covariates. The covariates were either continuous or discrete. If necessary, the dependent variable was transformed prior to analysis to enhance the normality of its distribution.[11] When a "best" model was fitted, according to the strategy outlined below, the test for significance of the group difference was then performed on the adjusted group means,[12] provided there were no significant interactions between group and any of the covariates. Group differences in the presence of interactions were assessed using stratification by different levels of the covariate(s) involved in the interaction.

Discrete Dependent Variables

Discrete dependent variables were analyzed by methods parallel to those used for continuous variables. For dichotomous variables, logistic regression was carried out by the BMDP®-LR program; for this analysis, the covariates could be either continuous or discrete. For polychotomous dependent variables, where the number of categories is three or more, log-linear modeling was performed by the use of the BMDP®-4F program. For this type of analysis, all covariates must be categorized. The logistic and log-linear models were fitted by the method of maximum likelihood.

To make the results parallel to those obtained by logistic regression, i.e., to maintain the distinction between dependent and independent variables, the marginals were fixed in the model[13] by incorporating the full k-factor interaction term involving the k covariates used in the model, effectively converting the log-linear model into a logit model. The significance of the relative risk for group was determined by examination of the appropriate model, as determined by the model that included all statistically significant effects and group, or by examination of the significant interactions. Adjusted relative risks were derived from the coefficients of the appropriate model.

Modeling Strategy

In each clinical category, many covariates were considered for inclusion in the statistical models for adjusted group contrasts. The large number of such covariates and consequent interaction terms and the resulting difficulties of interpretation obligated the adoption of a strategy for identifying a moderately simple model involving only significant effects. Interpretation of possible group differences was then made in the context of this simple model. A schematic representation of the generalized modeling strategy is provided in Figure D-1 of Appendix D.

An initial model including all two-factor interactions was examined. Global tests at the 0.05 level, or individual tests at the 0.15 level, were used to screen out unnecessary two-factor interactions. Thereafter, a hierarchical stepwise deletion strategy was used, eliminating effects with a p-value greater than 0.05 (except the main group effect) and retaining lower order effects if involved in higher order interactions, to result in the simplest model. Interactions between covariates, if significant, were retained as effects.

Occasionally, because of numerous covariates and the resulting sparse cell sizes, preliminary investigations of unadjusted and adjusted dependent variable-covariate associations were conducted to identify initial models using a subset of the original candidate covariates. These methods are specific to the dependent variables and the relevant covariates for a clinical area and are discussed in the individual chapters.

In the analysis for a particular dependent variable, when no group-by-covariate interactions were significant at the 0.05 significance level, adjusted group means or relative risks are presented. If any group-by-covariate interaction was significant at the 0.05 significance level, then the behavior of the group difference was explored for different levels (categories) of the covariate to identify the subpopulation(s) for which a group difference existed. Further, if any group-by-covariate interaction was significant at a level between 0.01 and 0.05, the adjusted group means or relative risks are also presented, after dropping the interaction term from the model.

Power

Conducting a statistical test using a Type I error, also called alpha level, of 0.05 (α=0.05) means that on the average, in 5 cases out of 100, a false conclusion would be made that an association (herbicide effect) exists when, in reality, there is no association. The other possible inference error (called a Type II error) is that of failing to detect an association when it actually exists. The probability of a Type II error (β) for a statistical test is 1 minus the power of the test. The power of the test is the probability that the test will reject the hypothesis of no herbicide effect when an effect does in fact exist. The power of a test depends on the group sample sizes, the disease prevalence rate, and the true group difference measured in terms of relative risk.

Table 7-2 contains the approximate sample size required to detect specific relative risks with an approximate power of 0.8 (β=0.2) using an alpha level of 0.05 for a two-sided test and assuming equal Ranch Hand and Comparison group sizes and unpaired analyses. Relative risk is the ratio of the disease prevalence rate of the Ranch Hand and Comparison groups. Conditions or diseases with Comparison population prevalence rates and exposed group relative risks corresponding to those below the heavy black line on the table can be detected with a probability of at least 0.8 with the sample sizes used in this study. That is, the sample sizes used for this study are greater than the sample size requirements appearing in this table below the heavy black line, implying a power of at least 0.8 in these situations. These tables imply that this study has adequate power to detect relative risks of 2.0 or more for major aggregates of disease such as heart disease and total cancer.

Table 7-3 provides the same information for continuous variables in terms of percentage mean shift and variability, assuming unpaired testing of a normally distributed variable and equal sample sizes.

In the 1987 followup of the AFHS, 995 Ranch Hands participated in the physical examination. In this size group, the chance of identifying zero cases of a disease with a prevalence of 1/500 or less is greater than 10 percent. Table 7-4 contains the probability of encountering no cases of disease states for cumulative prevalence rates of 1/200, 1/500, 1/1,000, 1/2,000, 1/5,000, and 1/10,000.

EXPOSURE INDEX ANALYSES

The exposure index was constructed to approximate the level of dose of the herbicide received by each member of the Ranch Hand group. Exposure index analyses were conducted to determine if differences existed in the levels of the dependent variable corresponding to the levels of the exposure index.

TABLE 7-2.

Required Sample Sizes to Detect Group Differences in Two-Sample Testing Assuming Equal Sample Sizes*
(Relative Risk Calculations)

Prevalence Rate of Disease in Comparison Population	Relative Risk (Multiplicative Factor of Prevalence Rate for Ranch Hand Group)										
	1.25	1.50	2.00	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00
$\frac{1}{10,000}$	2,822,082	783,901	235,164	78,384	43,544	29,391	21,944	17,415	14,393	12,243	10,640
$\frac{1}{5,000}$	1,410,882	391,901	117,564	39,184	21,766	14,691	10,968	8,703	7,193	6,118	5,317
$\frac{1}{1,000}$	281,922	78,301	23,484	7,824	4,344	2,931	2,187	1,735	1,433	1,218	1,058
$\frac{1}{500}$	140,802	39,101	11,724	3,904	2,166	1,461	1,089	863	713	606	526
$\frac{1}{100}$	27,906	7,741	2,316	768	424	285	211	167	137	116	100
$\frac{1}{50}$	13,794	3,821	1,140	376	206	137	101	79	65	54	47
$\frac{1}{10}$	2,504	685	199	62	32	20	14	10	7	5	4

*This study has unequal sample sizes; therefore, the tabled values are understated.

TABLE 7-3.

Required Sample Sizes to Detect Group Differences in Two-Sample Testing Assuming Equal Sample Sizes* (Mean Shift Calculations)

	Variability (σ/μ)				
Mean Shift	0.05	0.10	0.25	0.50	0.75
0.5%	1,568	6,272	39,200	156,800	352,800
1.0%	392	1,568	9,800	39,200	88,200
1.5%	175	697	4,356	17,423	39,200
2.0%	98	392	2,450	9,800	22,050
2.5%	63	251	1,568	6,272	14,112
5.0%	16	63	392	1,568	3,528
7.5%	7	28	175	697	1,568
10.0%	4	16	98	392	882

*This study has unequal sample sizes; therefore, the tabled values are understated.

TABLE 7-4.

Probability of Zero Cases as a Function of Prevalence

Disease Prevalence	Probability of Finding Zero Cases in a Group of 995 Participants
1/10,000	0.905
1/5,000	0.820
1/2,000	0.608
1/1,000	0.370
1/500	0.136
1/200	0.007

The exposure index was trichotomized as high, medium, and low, separately, for each of the three occupational groups (officer, enlisted flyer, enlisted groundcrew). Separate analyses were conducted for each occupational cohort, since relative differences in exposure between the groups could not be determined from historical records. Discrete dependent variables were evaluated using log-linear and logistic regression models, treating exposure level as a discrete variable (by means of two indicator variables) and adjusting for covariates. For continuous dependent variables, a general linear model was fit, adjusting for covariates and using two indicator variables to designate exposure level. Contrasts between medium and low, and between high and low exposure levels, were also performed.

The modeling strategy used for the exposure index analysis follows: First, the initial model did not include covariate-by-covariate interactions, and secondly, all the covariates were included as main effects in the final model. Further, in the presence of small frequencies of abnormalities, exposure index analyses were occasionally carried out using only the main effects model (i.e., using exposure index and all the covariates but not including interaction terms).

The terms significant, marginally significant, and borderline significant, as defined for the dependent variable-covariate associations, are used for the descriptions of the exposure index results.

LONGITUDINAL ANALYSES

General

Another objective of the AFHS is to observe and contrast the change in various laboratory parameters or the presence of abnormalities and disease between the Ranch Hand and the Comparison groups. This followup objective is not without scientific, logistic, and interpretive challenge, considering mobile populations, problems of loss to study, changing laboratory methods and diagnostic criteria, and the diversity of many changing factors over a period encompassing numerous followup examinations. The following sections describe the statistical procedures used for both continuous and discrete longitudinal data. In general, the analyses used data from two timepoints: Baseline and the 1987 followup. Tabulations include 1985 summary statistics in addition to those from Baseline and the 1987 followup for reference purposes. The summary statistics for the 1985 followup are limited to those participants included in the Baseline to 1987 longitudinal analysis who also participated in the 1985 followup examination.

Continuous Data

A repeated measures analysis of variance procedure[7] was used to analyze the variables measured on a continuous scale. The model describing the effects on the dependent variable (Y) for the kth participant (π_k) in the ith group (α_i) at the jth time (β_j) is as follows:

$$Y_{ijk} = \mu + \alpha_i + \pi_{k(i)} + \beta_j + \alpha\beta_{ij} + \varepsilon_{ijk}$$

The sources of variation and associated degrees of freedom are given below:

Source	Degrees of Freedom*
Group (Ranch Hand vs. Comparison)	1
Subject/Group	n_1+n_2-2
Time	1
Group-by-Time	1
(Subject-by-Time)/Group	n_1+n_2-2

*Based on n_1=944 Ranch Hands and n_2=1,113 Comparisons when no data are missing at either time endpoint for any participants.

The primary source of interest is the group-by-time interaction ($\alpha\beta_{ij}$). Using measurements on each participant at two times (Baseline and 1987 followup), a test on this interaction is equivalent to a test on the equality of mean differences (over time) between the Ranch Hand and Comparison groups.

Care must be taken in the interpretation of the main effect, time (β_j) (i.e., the difference in the means between the two timepoints). This effect is confounded by laboratory differences.

The source of variation due to group (α_i) reflects a difference between the overall Ranch Hand and Comparison means (averaged over both times). This source should complement the group difference findings at Baseline and at the 1987 followup, provided the group changes are consistent (no significant group-by-time interaction). All available participants were used in the group contrast analyses at each timepoint, whereas only the participants with both measures were included in the repeated measures analysis.

Discrete Data

Frequently, data were collected as normal-abnormal, or continuous measurements were discretized into this binomial response. For the Ranch Hand and Comparison groups, a Baseline versus 1987 followup 2x2 (normal-abnormal) table of frequencies was prepared (paired data):

Followup

Baseline	Ranch Hand: Abnormal	Ranch Hand: Normal	Comparison: Abnormal	Comparison: Normal
Abnormal		b		d
Normal	a		c	

As with the McNemar test,[8] only the Normal to Abnormal and Abnormal to Normal off-diagonal data were used in further contrasts. A conventional chi-square test was used to test the null hypothesis of a comparable pattern of change for the two groups (unpaired data).[14]

Pattern of Change

Group	Normal→ Abnormal	Abnormal→ Normal
Ranch Hand	a	b
Comparison	c	d

This test is equivalent to testing no group-by-time-by-endpoint interaction in a matched pair analysis.[15]

SUMMARY

The statistical methods and modeling strategies employed in this study are commonly applied in large cohort studies. The use of stepwise procedures and the descriptions of group-by-dependent variable-by-covariate interactions are also common to all large studies. The many analyses and corresponding tabulations have been prescribed in an analytical plan[16] and are intended to address many different approaches to data analysis and to allow the reader to check the results.

CHAPTER 7

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